



SPONGIFORM ENCEPHALOPATHY ADVISORY COMMITTEE
Minutes of the open session of the 89th meeting held on 22nd September
2005

Church House
Dean's Yard
Westminster
London
SW1P 3NZ

Members: Professor C. Higgins (Chair)
Dr. D. Brown
Professor N. Hooper
Mr. P. Jinman (Deputy Chair)
Professor C. Lasmézas
Professor J. Manson
Ms. D. McCrea
Professor G. Medley
Dr. P. Rudge

Assessors: Mr. A. Harvey (FSA)
Mrs. E. Lawrence (DH)

DA Assessors: Dr. M. Simmons (NAW)

Technical Advisors: Dr. P. Barrowman (Defra)
Dr. S. Dixon (FSA)
Dr. D. Matthews (VLA)
Dr. J. Stephenson (DH)
Professor J. Wilesmith (Defra)

SEAC Secretary: Miss K. Richards

Secretariat: Dr. T. Barlow
Dr. N. Ebenezer
Dr. P. Keep
Dr. V. Lund
Dr. C. Ravirajan

Also in attendance: Mr. P. Burke (Defra) and
Mr. P. Holley (FSA) for item 4.
Professor A. Colchester (University of Kent) for
item 5.

ITEM 1 – CHAIR’S INTRODUCTION

1. The Chair welcomed everyone to the 89th meeting of SEAC.
2. The SEAC Secretary explained to members of the public that it was the committee’s policy to conduct as much of its business as possible in open session. Holding open meetings allowed the public an opportunity to observe the committee at work and provided an insight into how an advisory committee provides independent scientific advice to Government. External experts and researchers involved in the studies that the committee will be considering are present. During the meeting the Chair may invite them to the committee table to present their work. Government officials are also present as members of the audience. As these officials are responsible for TSE policy in the various government departments they may also be invited to contribute to discussions.
3. The committee will also hold a reserved session in the afternoon to allow discussion of unpublished research on BSE in sheep and to be updated on current research at the Veterinary Laboratories Agency (VLA). This is in accordance with the SEAC Code of Practice.
4. Apologies for absence had been received from Professor Margaret Stanley and Dr Jacky Chambers. Mr John Bassett would attend the afternoon session. Members were reminded that they are obliged to declare any commercial or other interests they may have in the agenda items. The next meeting would be held on Thursday 24th November 2005 at the Roxburghe Hotel, Edinburgh.
5. The Chair announced that following a recruitment exercise Professor James Nicoll has joined SEAC to replace Professor Ironside. Professor Nicoll is Professor of Neuropathology at the University of Southampton and Consultant Neuropathologist at Southampton General Hospital and an expert in the field of neurodegeneration with considerable experience of clinical neuropathology. Unfortunately Professor Nicoll could not attend this meeting but will attend the November SEAC meeting.

ITEM 2 – APPROVAL OF MINUTES FROM SEAC 88 (SEAC 89/1) AND MATTERS ARISING

6. The minutes of the open session of the 30th June 2005 meeting were agreed as a correct record subject to the following amendments:
- paragraph 9, ninth bullet point, line 5, change “...relied...” to read “...relies...”
 - paragraph 11, line 6 change “...live diagnostic test for BSE...” to “...diagnostic test for BSE in live animals...”
 - paragraph 18, line 3 should read “Seprion Western blot test” lines 5, 7, and 12 change “Prep-specific” to “PrP-specific”
 - paragraph 21, line 2 change “...Byroad Platelet ...” to “...BioRad Platelia...”
 - paragraph 27, line 4 change “...differential diagnosis...” to “...definitive diagnosis...”
 - paragraph 33, first bullet point, line 6 change “...number of conditions...” to “...number of clinical conditions...”
 - paragraph 65, line 2 change “...genotyping should be combined if possible...” to “...genotyping data should be combined if possible for statistical analysis...”
 - paragraph 74, line 2 change “...confuse PrP^{Sc} with infectivity...” to “...confuse the amount of PrP^{Sc} protein with levels of infectivity...”

ITEM 3 – CURRENT ISSUES (SEAC 89/CURRENT ISSUES)

7. The committee was updated on the following issues:
- The Chair will meet the Executive Director of the European Food Safety Authority (EFSA) at the end of September 2005. The aim of the meeting is to develop a closer working relationship between SEAC and EFSA.
 - The current DH consultation on draft regulations is in preparation for full implementation of the Human Tissue Act (2004). The Chair proposed that SEAC should respond formally to the consultation in relation to any potential restrictions to TSE research from implementation of the draft regulations. The SEAC Secretary had sought the views of Professor James Ironside (NCJDSU), a past member of SEAC. Professor Ironside responded that the draft regulations restricted the use of organs, tissues, microscope slides and blocks of tissue, collected after 1 April 2006, from hospital autopsies for research or review without the consent of

relatives or a nominated individual. This may be problematic for retrospective review of autopsy material for public health purposes. It was agreed that SEAC would make a formal response to the consultation in relation to TSE research. The Secretariat would circulate a draft letter in response to the consultation along the lines suggested by Professor Ironside to members for comment.

- The Over Thirty Months Rule would be replaced by a BSE testing regime, expected to take effect from 7 November 2005.
- A Medical Research Council proposal to monitor the clinical effect of vCJD treatment with pentosan polysulphate had recently received ethical approval.
- The Cabinet Office Public Appointments Unit's newsletter aims to stimulate interest in public bodies such as SEAC. The Chair encouraged members to contribute to a possible future feature on the work of the committee by making themselves available for interview.
- Following advice from the CJD Incidents Panel (CJDIP), DH announced, on 20th July 2005, an extension of precautionary measures to reduce the risk of vCJD transmission through blood transfusion and surgical procedures. DH had notified around 100 people, who had donated blood to three people who later developed vCJD, that they may have a greater chance of being infected with vCJD compared with the general population. These people had been asked not to donate more blood or organs and to inform their medical practitioners before undergoing dental or surgical treatment. This notification procedure had gone smoothly. DH is awaiting the outcome of a CJDIP review of the risk to other recipients (about 1000) of blood from these donors.
- A TSE Joint Funders Group workshop on the research potential for TSE diagnostic tests in live animals including humans will be held on 13-14th December 2005. The Chair will attend and invited members to suggest other suitable attendees, especially from outside the TSE research community that might contribute to discussion about developing tests.
- Following the discussion at SEAC 88 on atypical cases of scrapie and possible implications for the National Scrapie Plan (NSP), the Chair wrote to Defra about the SEAC consideration

of this issue. The Chair will meet Defra policy officials and Veterinary Laboratories Agency (VLA) researchers in early November to discuss further research in this area. SEAC or its Sheep Subgroup will consider this issue further in the near future. An EFSA opinion on atypical scrapie is expected in mid-November 2005.

- A pre-publication copy of a paper¹ that suggests that evolutionary selection pressures may have maintained variation in the prion protein gene in sheep was circulated to members by email on 21 September 2005. Since the findings had potential implications for the NSP, members were invited to send comments to the Secretariat. Two independent experts would also be invited to comment. SEAC or its sheep subgroup will be asked to consider the paper in the future.
- A report² of preliminary findings of natural transmission of BSE between sheep in an experimental flock had been circulated to committee members. The committee considered it important to note that, to date, there has been no finding of naturally occurring BSE in surveillance of the national sheep flock. This research would be discussed further in the reserved business session.
- A report³ describing the use of an automated protein misfolding cyclic amplification (PMCA) technique to increase the amount of abnormal prion protein in blood samples of scrapie affected hamsters to a detectable level was considered. After PMCA, PrP^{Sc} had been detected in the blood of 16 out of 18 hamsters showing clinical signs of scrapie. A member commented that while the method did not appear to give false positives (PrP^{Sc} was not detected in the blood of any of the non-infected animals) it would be important to examine why PrP^{Sc} was not detected in two of the affected animals since false negative results would invalidate it as a screening test. It was noted that the authors suggested that, in these two samples, PrP^{Sc} may not have been sufficiently amplified. It was noted that the amplification phase of the test in the paper took several days to complete and the detection was by Western blot, a relatively insensitive detection method. The authors had suggested that to develop the test further, the

¹ Slate (in press) Molecular evolution of the sheep prion gene.

² Bellworthy *et al.* (2005) Natural transmission of BSE between sheep within an experimental flock. *Vet. Rec.* 157:206.

³ Castilla *et al.* (2005) Detection of prions in blood. *Nature Medicine published online 28/08/05.*

time taken for amplification could be shortened, and a more sensitive detection method used. The member considered it important to see if the method could detect PrP^{Sc} in the blood of pre-symptomatic animals. In addition, it would be important to verify that other laboratories could reproduce these results since some laboratories had reported unsuccessful attempts at repeating a version of the PMCA technique in the past. A member noted that laboratories in Italy and Germany had now successfully used the technique but with fewer rounds of amplification. It was also noted that the amplification step required normal brain tissue from the same species, which may hinder its use to screen human samples. Members concluded that this sensitive technique was potentially applicable to detection of abnormal prion protein in the blood of live animals or humans in preclinical stages of infection. However, it would require significant further development and evaluation before it could be used routinely. SEAC recommended that the method be considered at the TSE Joint Funders workshop on diagnostic test development.

- A very short report⁴ and a full report⁵ about the detection of abnormal prion protein and infectivity, respectively, in some tissues of the peripheral and central nervous systems (PNS and CNS) of BSE cases were circulated. It was noted that the findings could potentially have implications for specified risk materials (SRM) controls. The committee noted that the findings from each study were in single animals at the clinical stage of disease, and that the level of infectivity detected in PNS tissue was considerably lower than in CNS tissue. The issue would be discussed in more detail with unpublished data in the reserved business session.

ITEM 4 – EU TSE ROADMAP (SEAC 89/2)

8. The Chair informed the committee that Defra and FSA have asked SEAC to consider the European Commission TSE Roadmap, published on 15 July 2005.
9. Mr Patrick Burke (Defra) explained the background to the request and summarised the seven strategic goals outlined in the Roadmap. The Roadmap envisages amendments to EU TSE

⁴ Iwamaru *et al.* (2005) PrP^{Sc} distribution of a natural case of bovine spongiform encephalopathy. In *Prions. Food and Drug Safety*. Springer-Verlag, Tokyo, 2005.

⁵ Buschmann & Groschup (2005) Highly Bovine Spongiform Encephalopathy-sensitive transgenic mice confirm the essential restriction of infectivity to the nervous system in clinically disease cattle. *J. Infect. Dis.* 192, 934-942.

controls in light of the decline of BSE in Europe, taking into account new scientific evidence while continuing the aims of eradicating BSE and maintaining a high level of consumer protection. FSA and Defra are preparing for EU discussions on translating the Roadmap proposals into amendments to legislation. To inform these discussions, Defra and FSA asked the committee to consider whether the Commission has identified all of the risk issues that need to be taken into account. The committee was not asked to consider the age limit for removal of vertebral column since it considered this in detail at SEAC 85. It is intended that Defra and FSA will seek further, more detailed advice from SEAC in the future on specific proposals as they develop. While the Roadmap foresees changes to risk management measures, SEAC was asked to focus on whether any risk assessment issues have been omitted and whether additional scientific evidence is likely to be needed in support of changes to legislation.

10. The committee considered the strategic goals in turn.

Strategic goals for the short- and medium-term (2005 – 2009)

Specified risk material

11. The committee recommended that, since removal of SRM is a primary TSE-related public health protection measure, amendments to SRM controls should only be reviewed in light of emerging scientific findings on the distribution of TSE infectivity. Measures must maintain the current high level of consumer protection.

Feed ban

12. Members noted that appropriate feed controls are fundamental to prevent recycling of potentially infectious material in animal feed and re-emergence of a BSE epidemic. Any potential changes to feed controls should therefore be considered very carefully. Members suggested consideration should be given to assessment of the risks associated with the use of fishmeal in animal feed as it was unclear whether fish material would be sufficiently contaminated with BSE to present a risk. Since there is a great deal of movement of substances used in animal feed both within and into the EU, potential risks could arise from contaminated materials used in animal feed imported from outside the EU. This might also be an area that required further examination and risk assessment.

13. Members asked why animal feed contamination with bone fragments had been considered only in relation to beet pulp and not other root vegetables. It was explained that this was because beet was processed and used in the manufacture of animal feed. In contrast, other root vegetables were used, unprocessed, at a local level.
14. The committee was concerned that beet pulp should not be considered different from other root vegetables without supporting data. The committee considered it important to examine carefully all the constituents of animal feed, the sources of those materials, and then assess the potential TSE risks.

Monitoring programmes

15. The committee considered that appropriate surveillance is essential to monitor the potential impact of other changes to control measures. A member pointed out that measuring the cost of surveillance in terms of the number of positive cases detected did not reflect the importance of surveillance, and the cost might best be expressed in terms of the number of negative cases detected. It was considered that effective surveillance to ascertain infection prevalence was very important as a public health protection measure and an effective system should be maintained.

Categorisation of countries according to BSE risk

16. The committee considered that, both within and outside the EU, BSE surveillance regimes should be adequate in terms of numbers of animals tested and testing procedures used to evaluate the relative BSE risk between countries.

Review of culling policy with regard to TSEs in small ruminants

17. Members noted that culling could partly be driven by surveillance, but because of the widespread distribution of infectivity in small ruminants, culling could also be a consumer protection measure. One key consideration in the assessment of future culling policy appeared to be how often in the past other cases of the disease had been identified in the same flock through culling.
18. It was noted that whole flock culling may adversely affect the reporting of cases. The committee commented that, if maternal or intra-flock transmission was found to be significant in sheep,

this might impact on an assessment of culling as a risk reduction measure.

Cohort culling in bovine animals

19. The committee considered that it was important to determine the effectiveness of culling as a risk reduction measure and to consider whether culling a cohort (whether defined by feed or by birth) remained a proportionate response to risk in light of the declining BSE epidemic.

UK restrictions

20. The committee agreed that, as the numbers of BSE cases in GB have declined to similar levels found in the rest of Europe, this was a logical step. In response to a question about the report of the recent FVO mission to the UK, Mr Burke informed the committee that the report was likely to be published soon. Its conclusions were likely to be broadly favourable to the UK.

Strategic goal for the long term (2009-2014)

To modify measures in line with current technology and new evolving scientific knowledge

21. The committee agreed that it would be appropriate for SEAC, in the future, to look at the risks associated with modifying measures such as SRM rules, in the light of new scientific knowledge.
22. Members reiterated the view that it would be important to maintain effective surveillance to ascertain infection prevalence and to monitor the effect of changes to control measures. An appropriate level of surveillance of chronic wasting disease should be maintained in Europe.
23. Professor John Wilesmith (Defra) commented that, in deciding upon appropriate surveillance measures, it was necessary to decide upon the reason for the surveillance. Reasons include preventing diseased animals going into the food chain, to inform about the epidemiology of disease, or to detect the effectiveness of control measures.
24. Members suggested that, as a further strategic goal, surveillance programmes should be capable of monitoring potential changes to TSE prevalence, and of identifying new TSEs or other similar

diseases. There should also be mechanisms in place to deal with any changes detected.

25. In conclusion, SEAC welcomed the Roadmap and made three further general recommendations:
- changes to legislation in any one of the strategic areas might impact on other areas, therefore no single strategic area should be considered in isolation;
 - there should be a watching brief on emerging science that may impact on any of the measures under consideration.
 - in the event of any changes to TSE legislation it would be important to communicate effectively to consumers the reasons for change.

ITEM 5 – HYPOTHESIS ON THE ORIGIN OF BSE (SEAC 89/3)

26. The Chair introduced a paper by Colchester & Colchester (Lancet, 2nd September 2005)⁶ presenting a hypothesis that BSE was originally derived from a human TSE. The hypothesis suggested that, in the 1960s and 1970s, mammalian bone and carcass material used in animal feed was imported into the UK from the Indian sub-continent, particularly the area around the Ganges, and contained remains from humans infected with CJD.
27. The Chair explained that he and Mr Peter Jinman (Deputy Chair) had met with Professor Colchester (University of Kent) and Defra policy officials to discuss the paper prior to publication. The Chair thanked Professor Colchester for his willingness to discuss his hypothesis and for the professional manner in which the hypothesis was raised and presented, allowing a careful review of the issue. He thanked Professor Colchester for attending the SEAC meeting. The committee was asked to comment on the plausibility of the hypothesis and the areas of research to test the hypothesis suggested in the paper.
28. The Chair noted that from the discussions with Professor Colchester and Defra policy officials it was entirely possible that in the 1960s and 1970s animal feed from the Indian sub-continent was contaminated with human remains. Although this could not be proved unequivocally, there was good indirect evidence to suggest that this may have occurred, and that this was a

⁶ Colchester and Colchester (2005). The origin of bovine spongiform encephalopathy: the human prion disease hypothesis. *Lancet*. 366, 856-61.

plausible route of infection. However, the question remains, how likely is this route of infection? The committee should consider the likelihood of whether a human TSE jumped the species barrier to infect cattle, and the relative amount of such contaminated material which might have been fed to cattle compared with the amount of animal (sheep and cattle) carcasses which had been used in cattle feed, and the biochemical evidence for similarities/differences between human TSEs and BSE.

29. Members suggested that since prion infections are known to alter their properties to adapt to new host species, it might be impossible to establish the origin of BSE from the biochemical characteristics of prion strains. Currently it is not possible to predict the ability or likelihood of prion infections to cross species barriers based on a comparison of the biochemical properties of prion protein strains in two different species.
30. Dr Mike Simmons (National Assembly of Wales) asked whether it was more likely that BSE was originally derived from a scrapie strain or a human TSE. Members noted the possible origin of BSE from scrapie had been investigated very carefully but it had not been possible to determine whether or not BSE was originally derived from a scrapie strain. Dr Danny Matthews (VLA) noted that when sheep are infected with BSE by the oral route, on second passage in sheep no reduction in incubation period was observed. Therefore, it would appear that there is no significant species barrier for BSE infection from cattle to susceptible sheep. It was possible that there is also no species barrier for BSE transmission from sheep to cattle, but this was not known. It was also possible that BSE may have existed in sheep in the past but had not been detected. Members noted that, although BSE was known to be biochemically different from known scrapie strains, it was also different from sCJD and other prion strains. It was therefore not possible to establish biochemically whether BSE originated from CJD, scrapie or other known prion strains.
31. Members noted that, although little information was available on the relative amounts of human remains that could have contaminated animal feed in the past, in all probability only a small amount of human remains could reasonably have entered feed. In comparison, the quantities of animal remains that entered animal feed would have been very much larger. Furthermore, although the size of the species barrier between cattle and humans was unknown, it was likely that some barrier existed. Taking both of these factors into account it seemed

much more likely that the BSE epidemic originated from a disease in cattle or sheep rather than in humans.

32. A member pointed out that bone material from the Indian sub-continent was also exported to other countries, for example, Australia, yet this had not caused an outbreak of BSE in these countries. A member asked if this material was fed to cattle in India and, if so, why there was not a similar epidemic of BSE in that country. Professor Colchester responded that, as cattle feed was prepared and used on a local level, isolated cases of BSE might have occurred but such localised use would not result in an epidemic. Since there was no rigorous surveillance of BSE in cattle in India, isolated cases would not be detected. Dr Matthews informed the committee that, although there is a rendering industry in India, meat and bone meal would be fed mainly to poultry and pigs, but not cattle for religious reasons.
33. Members noted that Professor Colchester's work had highlighted the complex nature of production and movement of meat and bone meal and also the possibility of contamination of feed with human remains. Mr Burke explained that, although animal by-products from India were imported into the UK in the past and may have been contaminated with human remains, control measures implemented across the EU would now prevent the importation of such material for either feed or fertiliser. There are no EU approved rendering plants in India permitted to produce meat and bone meal for use in fertiliser in the EU. Professor Colchester asked for clarification about the controls on exports of such materials from India to the EU as well as about controls on imports reaching the UK. Mr Burke explained that exports to the EU were checked at border inspection posts, but the controls are rather complex and it would be better if Professor Colchester had a copy of his report. The Chair said this would be helpful.
34. The Chair asked the committee to comment on the areas of research to test the hypothesis suggested in the paper. A number were interesting scientifically but the committee should consider whether they might be important in terms of Government policy.
35. The committee agreed that examination of the transmission characteristics of human TSEs in transgenic mice expressing forms of the human and bovine prion protein gene, or a human CJD to cattle experiment, while potentially interesting, are unlikely to inform TSE controls and are therefore not essential to conduct. A member informed the committee that a number of experiments

to test the transmissibility of BSE, vCJD, sheep scrapie and sheep BSE in transgenic mice were underway to address different questions, and may inform the above question. These studies were using transgenic mice expressing human and bovine forms of the prion protein that had been produced in identical ways. Professor Colchester suggested that experiments in transgenic mice might be less clear than studies that examined transmissibility of human TSEs into cattle directly. Dr Stephenson reminded the committee that experimental feeding of human TSE material to animals was previously considered by SEAC to be unethical.

36. Members noted that investigations of historic production of animal feed were extremely difficult to undertake and had probably been investigated as much as possible. Although it was important to investigate possible feed related origins of BARB cases, further investigation of feed manufacture processes in the 1960s and 1970s would not be worthwhile. Appropriate controls now appear to be in place. The committee considered that the other areas of research suggested in the paper were not within SEAC's remit.

37. In summary, SEAC:

- was grateful that the hypothesis was raised and for the thoughtful and professional way in which Professor Colchester had raised the hypothesis with the committee,
- considered the hypothesis plausible but for a number of reasons considered that it was not the most likely origin of BSE,
- was reassured that control measures were in place to prevent possible transmission via the route identified in the hypothesis,
- considered that although a number of interesting areas of research had been identified, these were unlikely to affect policy, and that it was also unlikely that the hypothesis could be experimentally verified,
- agreed to produce a statement on the hypothesis.

ITEM 6 – SEAC EPIDEMIOLOGY SUBGROUP REPORT

38. Professor Graham Medley (Chair of SEAC Epidemiology Subgroup) updated the committee on the Subgroup's second meeting on 13th September 2005 which continued to address the SEAC request to evaluate the nature and profile of the vCJD epidemic. The Subgroup had reviewed the available data on the prevalence of vCJD infection in the UK population and modelling

studies, making extrapolations in areas where data gaps exist. The importance of data acquisition in removing uncertainty about the distribution of infection in the population had been highlighted. Whilst modelling methods are useful to explore hypotheses on, for example, the influence of age and genotype on infection, because the disease incubation period and the level of infection are unknown, any number of hypotheses were plausible. The validity of hypotheses could only be tested with further data. A position statement including a table of options for further data collection would be prepared with the aim of presenting it at SEAC 90. The Subgroup would meet early next year when further modelling work was completed.

39. The Chair asked whether the modelling work underway was sufficient to allow the Subgroup to address the questions SEAC had asked the Subgroup to consider. It was explained that modelling work was useful to provide quantification of uncertainties around the epidemic but it was crucial that more data were collected to remove these uncertainties and improve understanding of the epidemic.

ITEM 7 – BSE DVD

40. The Chair explained that during the SEAC 88 discussion on differential diagnosis of BSE, members expressed an interest in viewing the DVD supplied to veterinary surgeons on the clinical diagnosis of BSE in cattle.
41. Mr Burke informed the committee that the DVD had been produced by a clinical neurologist at VLA and circulated to a number of bodies including the State Veterinary Service, Meat Hygiene Service and organisations representing veterinary surgeons. The committee was shown extracts covering a number of diagnostic tests for BSE and differential diagnosis of BSE from other diseases with similar clinical signs.
42. Members welcomed the development of the DVD and noted it would be very useful in maintaining knowledge of the clinical symptoms of BSE, particularly amongst individuals who had not had practical experience of the disease at the height of the epidemic.

ITEM 8 – ANY OTHER BUSINESS

43. There was no other business.